Guidance for Industry

Draft Guidance for Industry: Amendment to "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products"

DRAFT GUIDANCE

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Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance is intended to amend the guidance entitled "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," dated May 2010 (2010 CJD/vCJD guidance)(May 27, 2010),[1] by revising the recommendations for labeling of plasma-derived products, including albumin and products containing plasma-derived albumin, to reflect current understanding of vCJD transmission through blood. When finalized, we will update the 2010 CJD/vCJD guidance by incorporating the revised labeling recommendations into the 2010 CJD/vCJD guidance, but will otherwise continue with our recommendations in the 2010 CJD/vCJD guidance as currently provided.

This guidance is intended for manufacturers of plasma-derived products, including albumin, and products containing plasma-derived albumin. Within this guidance, "you" refers to manufacturers and "we" refers to FDA.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

[1] This guidance is available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm.

II. BACKGROUND

CJD and vCJD are two forms of transmissible spongiform encephalopathy (TSE) affecting humans.[2] The Center for Biologics Evaluation and Research (CBER) first provided guidance for labeling of blood and blood products for CJD risk in November 1999, prior to reports of vCJD transmission by blood or plasma. We have continued to issue guidance on this topic as we continue to monitor epidemiological findings and other scientific data regarding CJD and vCJD. Since that time, four cases of presumed vCJD transmission by non-leukoreduced blood have occurred in the United Kingdom (U.K.). All of these were among recipients of blood from donors who later developed vCJD. In 2009, abnormal prion protein was discovered post mortem in the spleen tissue of a person with hemophilia[3] with no symptoms of vCJD or other neurological condition. The patient, who was over 70 years old, died of other causes. This individual had received blood transfusions and large amounts of U.K. plasma-derived Factor VIII. A risk assessment performed by U.K. health authorities concluded that, assuming that the abnormal prion protein finding was a marker for asymptomatic vCJD infection, the most likely source of such an infection was plasma-derived Factor VIII, rather than dietary exposure, endoscopy procedures, or red blood cell transfusions.[4]

In the 2010 CJD/vCJD guidance, in section VII.B., we recommended revised labeling of blood and blood components for transfusion to address the possible risk of transmission of vCJD as a potential risk. At that time, we also said that FDA intends to further address labeling of plasma derived products, including plasma derived albumin and products containing plasma derived albumin, in future recommendations. We now recommend revisions to labeling for plasma derivatives, including albumin, and products containing plasma-derived albumin, to reflect current knowledge that vCJD has been transmitted by blood, and most likely by a plasma derivative.

At this time, plasma derivatives have not been implicated in vCJD transmission in any country other than the U.K. In the 2010 CJD/vCJD guidance, we recommended preventive blood donor deferrals for time spent in the U.K. and in Europe, and for other risks of Bovine Spongiform Encephalopathy or vCJD exposure. To date, no U.S.-licensed plasma derived products have been manufactured from a donor known to have developed vCJD and no cases of vCJD been reported from use of a U.S.-licensed plasma derivative. In addition, published studies and information submitted to FDA show that certain plasma derivative manufacturing steps can remove TSE infectivity, although such experiments have inherent limitations (Refs. 1-3). However, based on animal studies, as well as on FDA risk assessments, the possibility of vCJD transmission by a U.S.-licensed plasma derivative, while extremely small, cannot be absolutely ruled out. For these reasons, the recommendations for labeling for plasma derivatives will include mention of vCJD for the first time, and the potential risk for its transmission. The recommended elements of

[2] For the purposes of this document, FDA considers the less common TSEs, Gerstmann-Sträussler-Scheinker syndrome and fatal insomnia syndromes, to be equivalent in risk to familial and sporadic CJD.
[3] Variant CJD and Plasma Products, Health Protection Agency (HPA), UK, http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733818681.
[4] vCJD Risk Assessment Calculations for a Patient with Multiple Routes of Exposure, HPA, Dept. of Health, UK, http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_100337.pdf.

the warning label for CJD are unchanged and continue to describe its transmission as a theoretical risk, given that there is no confirmed evidence that CJD is transmitted by blood (Refs. 4-7).

Similarly, we are recommending revisions to the labeling for plasma-derived albumin and products containing plasma-derived albumin. In addition to its indications for direct infusion into patients, albumin may be used in the manufacture of other biological products. For example, it is used in the culture media of certain licensed vaccines or as a stabilizer in certain recombinant clotting factor products. Licensed albumin and albumin contained in other licensed products have never been known to transmit viruses, CJD or vCJD, and laboratory experimental evidence suggests albumin is less likely to contain CJD-like agents when compared with other fractionated products (Refs. 8-10). There is no epidemiological evidence for transmission of CJD or vCJD in the U.S., U.K., or elsewhere by products containing plasma-derived albumin. Therefore, our recommendations for revised warning statements for vCJD risk for plasma-derived albumin and products containing plasma-derived albumin contain additional language to reflect the extremely low likelihood of vCJD and CJD transmission through these products.

In October 2010, we sought the advice of the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) on our proposed labeling recommendations to reflect potential risk of vCJD in plasma-derived products. TSEAC agreed unanimously that labeling for the potential risk of vCJD is warranted for plasma derivatives, including albumin and products containing albumin (Ref. 11).

When finalized, the recommendations set forth below are intended to supersede the recommendations in FDA's 2010 CJD/vCJD guidance at section VII.B (recommendations 2-4).

III. RECOMMENDATIONS

We recommend that you revise the statement in the Warnings and Precautions section of your labeling as follows:

Plasma-derived products Other than Albumin

"Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent."

Plasma-derived Albumin

"Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered

extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin."

Products Containing Plasma-derived Albumin

"This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products."

IV. REFERENCES

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3. Transmissible Spongiform Encephalopathies Advisory Committee Meeting Transcript, September 18-19, 2006, http://www.fda.gov/ohrms/dockets/ac/cber06.html#TransmissibleSpongiform.

4. Dorsey, K., Zou, S., et al. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion. 2009; 49: 977-84.

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